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Abstract: The members of the organic anion transporting polypeptide superfamily (OATPs) are classified within the SLCO solute carrier family. All functionally well characterized members are predicted to have 12 transmembrane domains and are sodium-independent transport systems that mediate the transport of a broad range of endo- as well as xenobiotics. Substrates are mainly amphipathic organic anions with a molecular weight of more than 300Da, but some of the known transported substrates are also neutral or even positively charged. Among the well characterized substrates are numerous drugs including statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antibiotics, antihistaminics, antihypertensives and anticancer drugs. Based on their amino acid sequence identities, the different OATPs cluster into families (in general with more than 40% amino acid sequence identity) and subfamilies (more than 60% amino acid identity). With the sequencing of genomes from different species and the computerized prediction of encoded proteins more than 300 OATPs can be found in the databases, however only a fraction of them have been identified in humans, rodents, and some additional species important for pharmaceutical research like the rhesus monkey (Macaca mulatta), the dog (Canis lupus familiaris) and the pig (Sus scrofa). These OATPs form 6 families (OATP1-OATP6) and 13 subfamilies. In this review we try to summarize what is currently known about OATPs with respect to endogenous substrates, tissue distribution, transport mechanisms, regulation of expression, structure-function relationship and mutations and polymorphisms.

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THE *SLCO* (FORMER *SLC21*) SUPERFAMILY OF TRANSPORTERS

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Abstract

The members of the organic anion transporting polypeptide superfamily (OATPs) are classified within the *SLCO* solute carrier family. All functionally well characterized members are predicted to have 12 transmembrane domains and are sodium-independent transport systems that mediate the transport of a broad range of endo- as well as xeno-biotics. Substrates are mainly amphipathic organic anions with a molecular weight of more than 300 Da, but some of the known transported substrates are also neutral or even positively charged. Among the well characterized substrates are numerous drugs including statins, ACE inhibitors, angiotensin receptor blockers, antibiotics, antihistaminics, antihypertensives and anticancer drugs. Based on their amino acid sequence identities, the different OATPs cluster into families (in general with more than 40% amino acid sequence identity) and subfamilies (more than 60% amino acid identity). With the sequencing of genomes from different species and the computerized prediction of encoded proteins more than 300 OATPs can be found in the databases, however only a fraction of them have been identified in humans, rodents, and some additional species important for pharmaceutical research like the rhesus monkey (*Macaca mulatta*), the dog (*Canis lupus familiaris*) and the pig (*Sus scrofa*). These OATPs form 6 families (OATP1–OATP6) and 13 subfamilies. In this review we try to summarize what is currently known about OATPs with respect to endogenous substrates, tissue distribution, transport mechanisms, regulation of expression, structure-function relationship and mutations and polymorphisms.

1. Introduction

Cells continuously need to take up nutrients as well as signaling molecules and to release metabolic endproducts for disposal. Most such substances, even if very lipopophilic, are not able to diffuse across plasma membranes and consequently need transport proteins to cross the cell boundaries. This is exemplified by cholesterol, which takes advantage of (transport) proteins to cross plasma membranes. For example, cholesterol absorption in the small intestine is mediated, at least in part, by the Niemann-Pick 1-like 1 (NPC1L1) protein (Lecerf and de Lorgeril, 2011), which is susceptible to inhibition by the drug ezetimibe. Else, release of cholesterol from the canalicular membrane of hepatocytes into bile is facilitated by the heterodimeric ATP-binding-cassette (ABC) transporter ABCG5/ABCG8 (Hazard and Patel, 2007). Bilirubin, the metabolic endproduct of the breakdown of heme, is practically water insoluble and has for a long time been assumed to enter hepatocytes by simple diffusion. While the issue of transmembrane movement of bilirubin was controversially discussed

(diffusion across lipid bilayer versus involvement of protein(s) (Ostrow et al., 1994)), several groups have now provided solid evidence for the involvement of organic anion transporting polypeptides (OATPs) in bilirubin uptake into hepatocytes (see below). From these prototypic results, it is safe to extrapolate that most substances and even highly non-polar or lipophilic compounds require transmembrane transport proteins to be moved between the extracellular space and the cytoplasm. The importance of transport proteins in the disposition of drugs is also gaining wide acceptance (Dobson et al., 2009; Fenner et al., 2012). The solute carrier superfamily (SLC) covers hundreds of proteins mediating the plasma membrane crossing of small molecules or solutes of various degrees of hydrophilicity and lipophilicity (Hediger et al., 2004). Among the SLC superfamily members, OATPs play a prominent role in transporting endo- as well as xeno-biotics including numerous drugs across plasma membranes.

In recent years, considerable progress has been made in identifying endogenous substrates of OATPs, in elucidating the roles OATPs play in drug disposition and transport of toxins, as well as in the characterization of genetic variants. In this overview on the current status of OATP research, we do not attempt to summarize the so far characterized drugs and xenobiotics, which have been identified as OATP substrates as this information can be found in several recent reviews (Fahrmayr et al., 2010; Giacomini et al., 2010; Hagenbuch and Gui, 2008; Kalliokoski and Niemi, 2009; Konig, 2011; Kusuhara and Sugiyama, 2009; Roth et al., 2012).

2. Phylogenesis of OATPs:

The first OATP, rat OATP1A1 (originally called Oatp) was isolated in 1994 using expression cloning (Jacquemin et al., 1994) and the first human OATP, OATP1A2 (originally called OATP) was isolated a year later by hybridization screening (Kullak-Ublick et al., 1995). In the following years several additional OATPs from humans and rodents were identified and characterized and we know today that there are eleven OATPs in humans. In 2004, an amino acid sequence based classification and nomenclature system was introduced and approved by the HUGO Gene Nomenclature Committee (Hagenbuch and Meier, 2004). This classification system allows us to name any newly identified OATP with a unique name if it is a unique member of the family or with the name of its already known orthologue. The general rules for this classification system are that proteins with more than 40 % identity belong to the same family while proteins with more than 60 % identity belong to the same subfamily (Hagenbuch

and Meier, 2004). On this basis, the human and rodent OATPs form 6 families (OATP1, OATP2, OATP3, OATP4, OATP5, and OATP6) and each family can have subfamilies (e.g. OATP1A, OATP1B, OATP1C). Within these subfamilies the individual OATPs are numbered according to the chronology of their identification and if there is already an orthologue known they are given the same number. The symbols for human and rodent proteins are always given in capitals (e.g. OATP1A2). The corresponding gene symbols begin with *SLCO* for human and *Slco* for rodents and have the same family number, subfamily letter and chronological number as the protein symbol (e.g. *SLCO1A2* for OATP1A2, *Slco1a1* for mouse OATP1A1). In contrast to protein symbols, gene symbols are always given in italics. However, it turned out that the 40% and 60% are not absolute numbers because e.g. *X. laevis* oatp1a2 has only 48% amino acid sequence identity to human OATP1A2 but based on phylogenetic analysis clearly is an orthologue of human OATP1A2 and does not belong to the 1B or 1C subfamily. Thus, newly identified OATPs should be carefully classified before a new name is assigned. The currently approved human members of the *SLCO* superfamily are summarized in Table 1. In the transporter classification database maintained by Milton Saier OATPs are found in the "The Organo Anion Transporter (OAT) Family" 2.A.60 (Saier et al., 1999).

Compared to the 52 members of the OATP superfamily reported in 2004, today more than 300 members have been identified and/or predicted from over 40 species. Figure 1 shows the phylogenetic tree of 70 OATPs from human, monkey, dog, pig, rat and mouse. The OATP1 family is the largest with 27 members, followed by the OATP6 family. In both families gene duplications in rodents resulted in several genes/proteins for rats and mice as compared to humans, while in subfamily OATP1B a gene duplication resulted in two genes/proteins for humans and monkeys (OATP1B1 and OATP1B3 as compared to rodent OATP1B2 or OATP1B4). The OATP3 family has the most conserved members with amino acid sequence identities between 94 and 99 % while the OATP6 family is the most diverged. It is interesting to note that no OATP homologues have been found in bacteria or yeast suggesting that OATPs are specific to the animal kingdom.

3. Endogenous substrates of OATPs

Murine OATP1A1, the founding member of the *SLCO* superfamily of organic anion transporters, was isolated with an expression-cloning approach using the anion bromosulphophthalein as substrate (Hagenbuch and Meier, 2004; Jacquemin et al., 1994).

Functional characterization of OATP1A1 in heterologous expression systems revealed that it can transport bile acids (e.g. cholate) and bile acid conjugates (e.g. taurocholate) (Eckhardt et al., 1999; Jacquemin et al., 1994) in a sodium-independent way with a preference for unconjugated over conjugated bile acids (Meier et al., 1997). Hence, bile salts can be considered the first identified endogenous OATP substrates. OATP1A2 can also transport unconjugated and conjugated bile acids (Table 2) (Kullak-Ublick et al., 1995). In addition, OATP1A2 can also transport dehydroepiandrosterone sulfate, a precursor for the synthesis of steroid hormones in many organs (Kullak-Ublick et al., 1998). Later, OATP1B1 (Abe et al., 1999), OATP1A2 and OATP4A1 (Fujiwara et al., 2001), OATP1C1 (Pizzagalli et al., 2002) and OATP3A1_v1 (Huber et al., 2007) were also found to transport thyroid hormones (Jansen et al., 2005). Additional endogenous OATP substrates are listed in Table 2.

To date, no severe human diseases related to bile salt homeostasis, to thyroid hormone biogenesis and metabolism or to steroid hormone synthesis have been linked to mutations in genes coding for various OATPs. Consequently, generation of *Slco* knockout mice was required to more directly prove and study the physiologic roles of OATPs in handling of endogenous substrates. Mammalian hepatocytes express two (humans) or three (rodents) different OATPs, which are members of the *SLCO* families 1A and 1B, respectively (Hagenbuch and Meier, 2004). The genes encoding these OATPs are clustered on human chromosome 12 and on mouse chromosome 6. Mice with a disrupted locus for *Slco1a/1b* subfamily members are vital and display no obvious disease phenotype, but have mildly elevated serum bile salt levels, supporting a role for OATPs in the hepatic uptake of bile salts (van de Steeg et al., 2010). Importantly, analysis of the bile salt pattern in the serum of these knock-out animals revealed unchanged levels of conjugated bile acids compared to the parent mouse strain but 13-fold elevated serum levels of unconjugated bile acids (van de Steeg et al., 2010). These findings were confirmed by another research group, which also reported elevated unconjugated bile acids but normal conjugated bile acids in mice with a disrupted *Slco1b2* gene (Csanaky et al., 2011). This latter finding is remarkable, as in general OATPs have overlapping substrate specificities (Table 2) and all rat orthologues of the mouse liver OATPs have been shown to transport bile salts in heterologous expression systems (Leuthold et al., 2009). Hence, *in vivo*, despite the coexpression of several OATPs in the same cells such as hepatocytes, a specific OATP may be required for the transport of a given substrate. If such an OATP is nonfunctional like in a knock-out mouse model or a human disease, the other OATPs do not seem to be capable in all instances to fully compensate for the loss of such

transport activity. After cloning of the human hepatocellular OATPs, two groups reported that OATP1B1 and OATP1B3 could mediate the transport of unconjugated bilirubin (Briz et al., 2003; Cui et al., 2001)(Table 2). Serum analysis of the knock-out mice lacking the OATP1A/1B family members revealed hyperbilirubinemia (van de Steeg et al., 2010). These animals display more than 40-fold elevated serum levels of total bilirubin compared to wild-type mice. About 95 % of the increased bilirubin was due to bilirubin mono- and bis-glucuronide, but also unconjugated bilirubin was elevated about 2.5-fold. Hence, this observation supports the concept that hepatocellular OATPs are involved in the transport of unconjugated and conjugated bilirubin into hepatocytes. Again, mice with an inactivated *Slco1b2* gene also have a mild hyperbilirubinemia (Csanaky et al., 2011; Zaher et al., 2008) suggesting that in mice, OATP1B2 plays a major role in bilirubin handling. The impact of the thyroid hormone transporter OATP1C1 on the disposition of thyroid hormones has lately been studied in knock-out mice. These animals have no alterations in their serum levels of thyroid hormones and their metabolites, but display reduced thyroxin levels and altered expression of deiodinases in their brains (Mayerl et al., 2012). These examples illustrate that knock-out mice are a powerful tool in the identification of endogenous or physiologic substrates of OATPs as well as in the explanation of human diseases with unknown etiology.

4. Tissue distribution

The expression of OATPs has been studied both at the mRNA and the protein level. In general, OATPs have been detected in essentially every organ in epithelial or endothelial cells. Some OATPs have a restricted expression and are therefore assumed to be organ specific, while others are expressed ubiquitously. Examples for such a restricted expression are the two human transporters OATP1B1 and OATP1B3 that are considered to be liver-specific (Roth et al., 2012) or the brain-specific OATP1C1 characterized in the rat (Sugiyama et al., 2003). Examples of ubiquitously expressed OATPs are the human OATP2A1, OATP3A1 and OATP4A1 whose mRNA was found in essentially all the tissues analyzed (Roth et al., 2012).

In humans, the OATP1 family has four members, OATP1A2, OATP1B1, OATP1B3 and OATP1C1 (Figure 1). Messenger RNA for *SLCO1A2* encoding OATP1A2 has been detected in numerous tissues including brain, kidney, liver, lung, testes, placenta and prostate (Roth et al., 2012). At the protein level, OATP1A2 has been shown to be expressed in endothelial cells of the blood-brain barrier (Bronger et al., 2005; Gao et al., 2000; Lee et al., 2005), at the

brush-border side in the distal nephron (Lee et al., 2005), in cholangiocytes (Lee et al., 2005), in the pars plana of the ciliary body epithelium (Gao et al., 2005), and in syncytiotrophoblasts (Loubiere et al., 2010) (Figure 2). As already mentioned above, OATP1B1 and OATP1B3 are considered to be liver specific transporters (Roth et al., 2012). Under normal conditions they are expressed at the sinusoidal membrane of human hepatocytes with OATP1B3 expression being stronger around the central vein than around the portal vein (Konig et al., 2000a). In a recent study protein expression of OATP1B1 and OATP1B3 was measured using a multiplex UPLC-MRM MS method and the results demonstrated that both proteins were found in equal amounts in membrane fractions isolated from human hepatocytes (Ji et al., 2012). *SLCO1B3* mRNA and OATP1B3 protein expression was also documented in several cancers (reviewed in (Obaidat et al., 2012)) and the high level of mRNA could be due to an alternatively spliced variant (Nagai et al., 2012). The last member in the OATP1 family, OATP1C1, is expressed in glial cells throughout the hypothalamus (Alkemade et al., 2011), at the blood-brain barrier, in the choroid plexus (Roberts et al., 2008), in Leydig cells of testes (Pizzagalli et al., 2002), and in the pars plana of the ciliary epithelium (Gao et al., 2005) (Figure 2).

The prostaglandin transporter, OATP2A1, is one of the ubiquitously expressed OATPs. *SLCO2A1* mRNA has been detected in almost every tissue tested (Roth et al., 2012). At the protein level, human OATP2A1 has been shown to be expressed in retinal epithelial cells and in epithelial and endothelial cell layers of different eye tissues including the ciliary body (Kraft et al., 2010) (Figure 2), in the endometrium (Kang et al., 2005), in neurons, astrocytes, and microglia (Choi et al., 2008), as well as in the parietal cells of the gastric corpus and the pyloric glands of the antrum (Mandery et al., 2010). The second transporter in the OATP2 family, OATP2B1 encoded by the *SLCO2B1 gene,* is also abundantly expressed in multiple organs at the mRNA level (Tamai et al., 2000). At the protein level OATP2B1 was detected at the sinusoidal membrane of hepatocytes (Kullak-Ublick et al., 2001), at the basolateral membrane of syncytiotrophoblasts (St Pierre et al., 2002), at the brush-border membrane in the small intestine (Kobayashi et al., 2003), in keratinocytes (Schiffer et al., 2003), in the mammary gland (Pizzagalli et al., 2003), at the luminal membrane of endothelial cells of the blood-brain barrier (Bronger et al., 2005), in the pars plicata and pars plana of the ciliary body (Gao et al., 2005; Kraft et al., 2010), in endothelial cells in the heart (Grube et al., 2006b), in human platelets (Niessen et al., 2009), and in the skeletal muscle (Knauer et al., 2010) (Figure 2).

SLCO3A1 mRNA levels were found in numerous tissues with highest levels in testes, brain, heart and lung (Huber et al., 2007). At the protein level, OATP3A1 is localized in the ciliary body epithelium (Gao et al., 2005), testes, in the choroid plexus, in neurons in the frontal cortex (Huber et al., 2007) and at the plasma membrane of epithelial cells of the lactiferous ducts in normal breast tissue (Kindla et al., 2011). In testes and in the brain two splice variants were shown to be expressed in a cell type-specific pattern (Huber et al., 2007). In testes, OATP3A1_v1 is expressed in germ cells while OATP3A1_v2 is expressed in Sertoli cells. In the choroid plexus variant 1 is expressed at the basolateral membrane while variant 2 is expressed at the apical and sub-apical membrane. In the frontal cortex, OATP3A1_v1 is localized in neuroglial cells of the grey matter and OATP3A1_v2 in cell bodies and axons of the neurons (Huber et al., 2007) (Figure 2).

SLCO4A1 mRNA was found in numerous tissues including the heart, placenta, lung, liver, skeletal muscle, kidney and pancreas (Fujiwara et al., 2001; Tamai et al., 2000). At the protein level OATP4A1 was detected in the ciliary body epithelium (Gao et al., 2005) and in syncytiotrophoblasts (Loubiere et al., 2010; Sato et al., 2003) (Figure 2). Based on northern blot analysis, OATP4C1 was predicted to be a kidney-specific transporter (Mikkaichi et al., 2004) but the human protein has not been localized yet. In addition, microarray studies suggest that mRNA from the *SLCO4C1* gene is also detectable in the liver (Bleasby et al., 2006).

SLCO5A1 mRNA was reported in fetal brain, prostate, skeletal muscle and thymus (Bleasby et al., 2006). At the protein level, OATP5A1 was detected at the plasma membrane of epithelial cells of the lactiferous ducts in normal breast tissue (Kindla et al., 2011).

The expression of *SLCO6A1* mRNA was detected in testes, spleen, brain and placenta (Lee et al., 2004; Suzuki et al., 2003). The expression of the different OATPs in various tumors has recently been summarized (Obaidat et al., 2012).

5. Transport Mechanisms of Oatps

The mechanism(s) by which OATPs transport is(are) not fully understood, but OATPs are believed to act as organic anion exchangers (Hagenbuch and Gui, 2008). In 1997 bicarbonate was identified as the first counterion in experiments with rat OATP1A1 expressed in HeLa cells (Satlin et al., 1997). Additional experiments demonstrated that reduced glutathione and

glutathione conjugates could act as counter ions. Transport of taurocholate and leukotriene C_4 mediated by rat OATP1A1 was trans-stimulated by glutathione (Li et al., 1998), while taurocholate transport by rat OATP1A4, but not by rat OATP1A1, was also trans-stimulated by the efflux of a conjugate of glutathione (Li et al., 2000), suggesting that no general transport mechanism exists for OATPs. OATP1B3 mediated cotransport of glutathione (Briz et al., 2006) could not be confirmed (Mahagita et al., 2007) and such a transport mechanism would be hard to reconcile for the uptake of organic anions into hepatocytes given the rather steep in-to-out glutathione gradient across the hepatocyte plasma membrane.

Uptake by various OATPs has been shown to be stimulated by a low extracellular pH, such as for example transport mediated by OATP2B1, which in expressed among other organs in the small intestine (Kobayashi et al., 2003). The influence of extracellular pH was tested with 13 different OATPs, out of which 12 were stimulated by a low extracellular pH. This stimulation was found to be due to a lowered K_m value at pH 6.5 compared to pH 7.4 demonstrating increased affinity of the transport process at low pH. Mutagenesis of a highly conserved histidine in the third transmembrane domain to a glutamine abolished the pH dependency of rat OATP1A1. In contrast, replacing the glutamine found at this conserved position in the pH-insensitive OATB1C1 with a histidine rendered OATP1C1 pH sensitive (Leuthold et al., 2009). Hence, an acidic microclimate like in the intestine or lowering the pH in the microclimate adjacent to OATPs by an active Na^+/H^+-exchanger could stimulate their transport compared to uptake at neutral pH.

In addition to this modulation of transport at low pH, i.e. at higher proton concentrations, a similar modulation of OATP mediated substrate uptake by another substrate has also been observed. This was first reported for rat OATP1A4, where estradiol-17β-glucuronide stimulated transport of taurocholate but not of digoxin (Sugiyama et al., 2002). A similar stimulation has also been observed for OATP2B1, where prostaglandins A1 and A2 stimulated the transport of dehydroepiandrosteron sulfate (Pizzagalli et al., 2003). Interestingly, OATP2B1-mediated transport of dehydroepiandrosterone and estrone-3-sulfate was stimulated at low progesterone concentrations, while at higher concentrations of progesterone as modulator transport activity returned to control values (Grube et al., 2006a). In the same study, testosterone and mifepristone inhibited rather than stimulated transport activity of OATP2B1. Dietary and herbal components have also been documented to stimulate OATP-mediated transport, such as rutin, which stimulated OATP1B1-mediated

dehydroepiandrosterone sulfate uptake (Wang et al., 2005) and green tea extracts or the green tea epigallocatechin gallate, which stimulated OATP1B3-mediated uptake of estrone-3-sulfate (Roth et al., 2011). Finally, OATP1B3, but not OATP1B1-mediated transport of estradiol-17β-glucuronide was stimulated by clotrimazole (Gui et al., 2008). However, such a stimulation was not observed for estrone-3-sulfate transport, which was not affected by clotimazole or for fluo-3 transport, which was inhibited. Several additional drugs tested in this study did not stimulate either OATP1B1 or OATP1B3. These results clearly show that OATPs have more than one substrate binding site, which may or may not interact with each other. This has been formally demonstrated with kinetic experiments that revealed a high and a low affinity component for estrone-3-sulfate uptake for OATP1B1 (Gui and Hagenbuch, 2009; Noe et al., 2007; Tamai et al., 2001). In summary, the transport mechanism of OATPs is complex, may vary for the same transporter for different substrates and clearly more work is needed to elucidate it in detail.

Understanding the exact transport mechanisms of OATPs is highly relevant as depending on the transport mechanism, OATPs may or may not be able to concentrate a substrate within cells over the respective extracellular concentration, like for example drugs in hepatocytes. For illustration, the concentration of the antidiabetic drug glibenclamide is 50 times higher in rat livers than in plasma (Kellner et al., 1969). While glibenclamide has been shown to be transported by OATP2B1 (Fuchikami et al., 2006), for OATP1B1 and OATP1B3 only inhibition by glibenclamide, but not direct uptake, has been demonstrated (Bednarczyk, 2010). We would like to emphasize that although such inhibition indicates that glibenclamide could be a substrate of OATP1B1 and/or OATT1B3 it does not necessarily imply that it is a substrate. This has recently been worked out for the liver function test marker indocyanine green, which is a potent inhibitor of all three hepatocellular OATPs and of the sodium taurocholate cotransporting polypeptide NTCP, but is only transported by NTCP and OATP1B3 (de Graaf et al., 2011).

6. Regulation of expression and modulation of function:

Regulation of OATP expression has been documented at the transcriptional as well as at the post-translational level. Early studies demonstrated that expression of the liver specific OATP1B1 and OATP1B3 was controlled by the liver enriched hepatocyte nuclear factor 1α (HNF1α) (Jung et al., 2001). In hepatocellular carcinoma (HCC), expression of OATP1B3 was shown to be decreased while expression of OATP1B1 was normal at the mRNA level or

slightly decreased at the protein level (Cui et al., 2003; Vavricka et al., 2004). It was also shown that HNF3β, which was overexpressed in HCC, could repress transcriptional expression of OATP1B3 but not of OATP1B1, potentially explaining the selective down-regulation of OATP1B3 in HCC (Vavricka et al., 2004). It is interesting to note that in ovarian cancer, but not in healthy ovarian tissue, expression of the liver specific OATP1B1 and OATP1B3 was reported (Svoboda et al., 2011). In addition several transcription factors in the family of the nuclear receptors have been shown to regulate OATP expression. Studies in breast carcinoma and breast cancer cell lines demonstrated a positive correlation between human PXR and OATP1A2 expression (Miki et al., 2006). This correlation was confirmed and a direct effect of PXR activity on OATP1A2 expression could be demonstrated (Meyer zu Schwabedissen et al., 2008). The same study also confirmed that the *SLCO1A2* promoter could be activated by the constitutive androstane receptor (CAR) (Meyer zu Schwabedissen et al., 2008). Using isolated human hepatocytes it was shown that treatment with the prototypic activator of the aryl hydrocarbon receptor (AhR) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and with the CAR activator phenobarbital resulted in a decreased expression of OATP1B3 and OATP2B1 (Jigorel et al., 2006). The promoter of human *SLCO4C1* was also activated via AhR by 3-methylcholanthrene and by fluvastatin (Suzuki et al., 2011). Oltipraz, which activates NFE2-related factor 2 (Nrf2), also down-regulated OATP1B3, while the PXR agonist rifampicin led to an increase of OATP1B1 (Suzuki et al., 2011). Furthermore, OATP1B1 was shown to be regulated by the liver receptor α (LXRα) and by the farnesoid X receptor (FXR) (Meyer Zu Schwabedissen et al., 2010) and earlier it was also shown that OATP1B3 is under the control of FXR (Jung et al., 2002). In addition to these studies there are many other reports that show that OATP expression is influenced by different growth factors, cytokines and chemicals. Hepatocyte growth factor (HGF) down-regulated *SLCO1B1* and *SLCO2B1* mRNA and protein while mRNA for *SLCO1B3* was not affected (Le Vee et al., 2009). Similarly, down-regulation of *SLCO1B1*, *SLCO1B3* and *SLCO2B1* mRNA as well as OATP1B1 at the protein level was shown by interleukin 1β (Le Vee et al., 2008).

Post-translational regulation was demonstrated for OATP2B1. Protein kinase C activation by a phorbol ester resulted in increased phosphorylation of OATP2B1 with a decrease in maximal transport rate suggesting a rapid internalization of the transporter (Kock et al., 2010).

All these regulations at the transcriptional and post-translational levels could lead to increased or decreased OATP-mediated uptake. However, as outlined above, modulation of OATP-

mediated transport could also be due to direct effects of substances, e.g. by acting from the cis-side either as inhibitors or as stimulators of substrate transport. Furthermore, several of these modulators have been shown to act in a substrate-dependent way, making predictions of potential interactions more complicated. For example, rifampicin at 10 μM had no effect on OATP1B1-mediated uptake of bromosulfophthalein (BSP) (Vavricka et al., 2002) but inhibited estradiol-17β-glucuronide uptake by 90 % (Tirona et al., 2003). In another study, 100 μM gemfibrozil inhibited OATP1B1-mediated uptake of taurocholate, fluvastatin and simvastatin by about 60 % but had no effect on the uptake of estrone-3-sulfate or troglitazone-sulfate (Noe et al., 2007). Clotrimazole, epigallocatechin gallate, diclofenac and ibuprofen are among the chemicals that have been shown to have stimulatory, inhibitory or no effects on OATP-mediated transport in a substrate-dependent way (Gui et al., 2008; Kindla et al., 2011; Roth et al., 2011). Thus, because the molecular mechanisms of these modulations are not known yet it is crucial to test more than just a single OATP substrate when screening for potential interactions, e.g. to predict pharmacokinetic interactions during drug development.

7. Structure function relationship:

Based on hydrophobicity analyses, experimental data available from rat OATP1A1 (Jacquemin et al., 1994; Wang et al., 2008) and homology modeling, OATPs are 12 transmembrane domain proteins with the amino- and the C-terminal ends located at the cytoplasmic side of the membrane (Figure 3A). Because so far no crystal structure data are available, homology modeling was used to predict a putative three-dimensional model (Figure 3B). Furthermore, several groups have used chimeric approaches combined with site-directed mutagenesis and homology modeling to investigate what regions or what amino acids would be important for OATP function. Based on such studies it became clear that cysteine residues in the large extracellular loop 5 are involved in disulfide bonds and are required for proper surface expression of OATP2B1 (Hanggi et al., 2006) (Figure 3A). Transmembrane domains 1, 8, 9 and 10 as well as extracellular loop 6 have been shown to be important for OATP1B1 and OATP1B3 substrate transport (Degorter et al., 2012; Gui and Hagenbuch, 2008, 2009; Miyagawa et al., 2009). Furthermore, site-directed mutagenesis of conserved positively charged amino acids identified several residues in transmembrane domains 1, 7 and 10 that affect substrate transport in OATP1B1 and OATP1B3 (Glaeser et al., 2010; Mandery et al., 2011; Weaver and Hagenbuch, 2010). A recent study demonstrated that when the three amino acids A45, L545 and T615 in OATP1B1 were replaced to their corresponding residues in OATP1B3, OATP1B1 was able to transport the OATP1B3-selective substrate

cholecystokinin-8 (CCK-8) (Degorter et al., 2012), suggesting that these amino acids are indeed involved in substrate recognition or transport by OATP1B3. These studies are important because they will help to eventually understand the molecular mechanisms of the broad substrate specificity of OATPs and potentially allow predicting and thus preventing drug-drug interactions at the OATP levels.

8. Mutations and Polymorphisms of OATPs

So far, few pathophysiologic conditions related to mutations in *SLCO* genes have been reported. Mesolemia-synosteses syndrome (OMIM600383) is a rare disease and includes mesomelic limb shortening and acral synosthoses (Isidor et al., 2009). This syndrome has been linked to a disturbance in sulfate metabolism and/or homoestasis (Dawson, 2011). Cytogenetic analysis of 5 patients from four families with this disease identified a submicroscopic microdeletion on chromosome 8q13 (Isidor et al., 2010). This deletion spans the two genes *SULF1* (heparin sulphate 6-O-endosulfatase 1) and *SLCO5A1* (OATP5A1). OATP5A1 is expressed in adult heart and in fetal brain and heart (Isidor et al., 2010), but its function has not been characterized so far. As in all patients deletions spanned both the *SULF1* and the *SLCO5A1* gene, the contribution of missing or malfunctioning OATP5A1 remains to be worked out, in particular as in a single healthy individual a partial deletion of *SLCO5A1* was reported (de Smith et al., 2007). Rotor syndrome is a rare, benign syndrome presenting with conjugated and unconjugated hyperbilirubinemia in conjunction with coproporphyrinuria and a massively altered BSP clearance (Strassburg, 2010). Its inheritance is autosomal recessive. A recent investigation of individuals with Rotor syndrome from eight different families revealed mutations in the *SLCO1B1* and *SLCO1B3* genes, rendering the respective OATPs non-functional (van de Steeg et al., 2012). Mice with a disrupted *Slco1a/1b* locus also presented with unconjugated and conjugated hyperbilirubinemia. (van de Steeg et al., 2012). A study with healthy volunteers associated elevated conjugated and unconjugated bilirubin with the *15 allele of *SLCO1B1*, which is known to display reduced transport activity of the corresponding protein (Zhang et al., 2007). A study investigating the effect of the p.V174A variant of OATP1B1 on thyroid and estrogen metabolite levels in serum found total bilirubin, estrone-3-sulfate and thyroxine sulphate levels to be higher in individuals with the p.174A variant (van der Deure et al., 2008a). A genome-wide association study associated *SLCO1B3* variants with elevated total and unconjugated serum bilirubin (Sanna et al., 2009), while a meta-analysis of three studies associated a *SLCO1B1* variant with elevated serum bilirubin (Johnson et al., 2009). The finding of the latter study was recently confirmed in an

independent genome-wide association study (Bielinski et al., 2011). Hence, there is now ample genetic evidence for a role of OATP1B1 and OATP1B3 in hepatocellular uptake of unconjugated and conjugated bilirubin. Finally, serum levels of reverse triiodothyronine have also been reported to be elevated in carriers of the OAPT1A2 p.172D variant (van der Deure et al., 2010).

A genome-wide association study in a cohort of individuals with progressive supranuclear palsy found a suggestive association with *SLCO1A2* in addition to other loci (Hoglinger et al., 2011). Additionally, a genome-wide association study of Crohn's diseases in an Ashekenazi Jewish population found a variant of the *SLCO6A1* to be disease associated (Kenny et al., 2012).

While evidence for the involvement of *SLCO* genes in the pathogenesis of diseases is starting to emerge, a multitude of studies have investigated the role of *SLCO* variants on drug disposition with a particular focus on pharmacokinetics of drugs. Many reviews have covered the role of genetic *SLCO* variants on pharmacokinetics of drugs (Fahrmayr et al., 2010; Franke et al., 2010; Kerb, 2006; Konig, 2011; Niemi et al., 2011; Sissung et al., 2010; Stieger and Meier, 2011; Zair et al., 2008). Understanding the impact of *SLCO* pharmacogenomics is not only relevant for understanding alterations in pharmacokinetics of drugs in patients with different *SLCO* genotypes (Kalliokoski and Niemi, 2009), but also contributes to an understanding of adverse drug reactions. This is exemplified in the case of *SLCO1B1*, which in an elegant genome-wide association study was associated with simvastatin-induced myotoxicity (Link et al., 2008). This and other studies have been the basis to suggest a dosing regimen for statins, which takes the *SLCO1B1* genotype into account (Niemi, 2010).

9. Conclusion and Outlook

Since the cloning of the first OATP, the *SLCO* family members have made it to center stage in drug development (Giacomini et al., 2010) and in the understanding of drug disposition (Fenner et al., 2012). While the progress in developing tools for understanding the role of OATPs in handling of endo- and xenobiotics has been enormous, knowledge on their molecular transport mechanisms and on their structure is clearly lagging behind. Both areas are however highly relevant for developing better models to predict their impact in physiology and pathophysiology as well as in drug disposition. In addition, OATPs are increasingly

recognized as important transporters in cancer therapy (Obaidat et al., 2012) and in understanding clearance tests like e.g. liver function tests (Stieger et al., 2012).

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Table 1: The human members of the organic anion transporting superfamily

New gene symbol	New protein name	Predominant substrates	Tissue distribution/subcellular expression	Link to disease	Human gene locus	Sequence Accession ID	Splice variants
SLCO1A2	OATP1A2	Bile salts, organic anions and cations	Brain (endothelial cells), kidney (apical), intestine (apical), liver (cholangiocytes), eye (ciliary body)		12p12	NM_021094 NM_134431	2 splice variants
SLCO1B1	OATP1B1	Bile salts, organic anions	Liver (hepatocytes)	(Statin-induced myopathy, Rotor Syndrome)	12p	NM_6446	
SLCO1B3	OATP1B3	Bile salts, organic anions	Liver (hepatocytes)	(Unconjugated hyperbilirubinemia, Rotor syndrome)	12p12	NM_019844	
SLCO1C1	OATP1C1	T4,T3, rT3	Brain (blood-brain barrier), testis (Leydig cells)		12p12.2	NM_017435 NM_001145944 NM_001145945 NM_001145946	4 splice variants
SLCO2A1	OATP2A1	Prostaglandins (C/lactate)	Ubiquitous		3q21	NM_005630	
SLCO2B1	OATP2B1	E-3-S, DHEAS	Liver (hepatocytes), placenta, intestine (apical), eye (ciliary body)		11q13	NM_007256 NM_001145211 NM_001145212	3 splice variants

Table 2: Endogenous substrates of organic anion transporting polypeptides

If K_m-values are available, data demonstrating transport are omitted. Endogenous concentrations are given for systemic concentration and are, due to space reasons, not necessarily found in the references given in this table. The concentrations found for many substances in plasma vary widely (in some instances more than factor of 10). In addition, many of the listed substance have a considerable binding to plasma proteins. Consequently, the values given should only be taken as approximate.

Transporter	Substrate	Affinity	Plasma concentration	Reference
Rat				
OATP1A1	cholate	54 μM	~ 3 μM	(Eckhardt et al., 1999)
	taurocholate	32 – 50 μM	~ 1 μM	(Eckhardt et al., 1999; Kullak-Ublick et al., 1994; Satlin et al., 1997)
	glycocholate	54 μM	~ 0.1 μM	(Eckhardt et al., 1999)
	taurochenodeoxycholate	7 μM	~ 0.1 μM	(Eckhardt et al., 1999)
	tauroursodeoxycholate	13 μM	~ 0.01 μM	(Eckhardt et al., 1999)
	bilirubinmonoglucuronide		~ 1 μM	(Reichel et al., 1999)
	dehydroepiandrostenone sulfate	5 μM	~ 0.1 nM	(Eckhardt et al., 1999)
	aldosterone	15 nM	~ 0.1 nM	(Bossuyt et al., 1996a)
	cortisol	13 μM	~ 0.1 μM	(Bossuyt et al., 1996a)
	estradiol-17β-glucuronide	3 - 20 μM		(Bossuyt et al., 1996a; Eckhardt et al., 1999; Ishizuka

				et al., 1998; Kouzuki et al., 1999)
	Estrone-3-sulfate	5 - 12 μM		(Bossuyt et al., 1996a; Eckhardt et al., 1999)
	Leukotriene C_4		~ 1 pM	(Li et al., 1998)
	diiodothyronine (T2)			(Friesema et al., 1999)
	diiodothronine sulfate (T2S)			(Friesema et al., 1999)
	prostaglandine E_2	pH 6.5	~ 1 nM	(Leuthold et al., 2009)
	triiodothyronine (T3)		~ 1 nM	(Friesema et al., 1999)
	triiodothyronine sulfate (T3S)		~ 0.1 nM	(Friesema et al., 1999)
	reverse triiodothyronine (rT3)		~ 0.01 nM	(Friesema et al., 1999)
	reverse triiodothyronine sulfate (rT3S)		~ 0.1 nM	(Friesema et al., 1999)
	thyroxine (T4)		~ 50 nM	(Friesema et al., 1999)
	thyroxine sulphate (T4S)		~ 0.05 nM	(Friesema et al., 1999)
OATP1A3	taurocholate	10-31 μM	~ 1 μM	(Masuda et al., 1999; Takeuchi et al., 2001)
	dehydroepiandrostenone sulfate	9 – 17 μM	~ 0.1 nM	(Reichel et al., 1999; Takeuchi et al., 2001)
	estradiol-17β-glucuronide	3-35 μM		(Noe et al., 1997; Takeuchi et al.,

				2001)
	estrone-3-sulfate	11-15 μM		Noe, 1997 #333}(Takeuchi et al., 2001)
	thyroxine (T4)	7-20 μM	~ 50 nM	Abe, 1999 #670}(Takeuchi et al., 2001)
	triiodothyronine (T3)	6-44 μM	~ 1 nM	(Abe et al., 1999; Takeuchi et al., 2001)
OATP1A4	cholate	46 μM	~ 3 μM	(Noe et al., 1997)
	taurocholate	35 - 36 μM	~ 1 μM	(Abe et al., 1999; Noe et al., 1997)
	glycocholate	40 μM	~ 0.1 μM	(Reichel et al., 1999)
	taurochenodeoxycholate	12 μM	~ 0.1 μM	(Reichel et al., 1999)
	tauroursodeoxycholate	17 μM	~ 0.01 μM	(Reichel et al., 1999)
	dehydroepiadrostenone sulfate	17 μM	~ 0.1 nM	(Reichel et al., 1999)
	estradiol-17β-glucuronide	3 μM		(Noe et al., 1997)
	estrone-3-sulfate	11 μM		(Noe et al., 1997)
	prostaglandine E_2	pH 6.5	~ 5 nM	(Leuthold et al., 2009)
	triiodothyronine (T3)	6 μM	~ 1 nM	(Abe et al., 1999)
	thyroxine (T4)	7 μM	~ 50 nM	(Abe et al., 1999)
OATP1A5	cholate	9 μM	~ 3 μM	(Walters et al., 2000)
	taurocholate	18 – 30 μM	~ 1 μM	(Abe et al., 1999; Walters et al.,

				2000)
	glycocholate	15 μM	~ 0.1 μM	(Walters et al., 2000)
	taurochenodeoxycholate	7 μM	~ 0.1 μM	(Walters et al., 2000)
	glycochenodeoxycholate	6 μM		(Walters et al., 2000)
	tauroursodeoxycholate	7 μM	~ 0.01 μM	(Walters et al., 2000)
	glycoursodeoxycholate	5 μM		(Walters et al., 2000)
	taurodeoxycholate	6 μM	~ 0.1 μM	(Walters et al., 2000)
	glycodeoxycholate	4 μM		(Walters et al., 2000)
	dehydroepiandrostenone sulfate	162 μM	~ 0.1 nM	(Cattori et al., 2001)
	estradiol-17β-glucuronide	39 μM		(Cattori et al., 2001)
	estrone-3-sulfate	268 μM		(Cattori et al., 2001)
	leukotriene C_4		~ 1 pM	(Cattori et al., 2001)
	prostaglandine E_2	35 μM	~ 5 nM	(Cattori et al., 2001)
	thyroxine (T4)	5 μM	~ 50 nM	(Abe et al., 1999)
	triiodothyronine (T3)	7 μM	~ 1 nM	(Abe et al., 1999)
OATP1B2	taurocholate	9 – 27 μM	~ 1 μM	(Cattori et al., 2000; Kakyo et al., 1999)
	dehydroepiadrostenone sulfate	5 μM	~ 0.1 nM	(Cattori et al., 2001)

	estradiol-17β-glucuronide	32 μM		(Cattori et al., 2001)
	estrone-3-sulfate	37 μM		(Cattori et al., 2001)
	arachidonate	96 μM	~ 10 μM	(Kanai et al., 1995)
	CCK8	15 μM	~ 1 pM	(Ismair et al., 2001)
	leukotriene C_4	7 μM	~ 1 pM	(Cattori et al., 2001)
	prostaglandine E_2	13 μM	~ 5 nM	(Cattori et al., 2001)
	triiodothyronine (T3)		~ 1 nM	(Cattori et al., 2000)
	thyroxine (T4)		~ 50 nM	(Cattori et al., 2000)
OATP1C1	taurocholate		~ 1 μM	(Sugiyama et al., 2003)
	CCK-8		~ 1 pM	(Sugiyama et al., 2003)
	estradiol-17β-glucuronide	11 μM		(Sugiyama et al., 2003)
	estrone		~ 0.1 nM	(Sugiyama et al., 2003)
	estrone-3-sulfate			(Sugiyama et al., 2003)
	dehydroepiandrostenone sulfate		~ 0.1 nM	(Sugiyama et al., 2003)
	dihydrotestosterone		~ 1 nM	(Sugiyama et al., 2003)
	leukotriene C_4		~ 1 pM	(Sugiyama et al., 2003)
	leukotriene E_4			(Sugiyama et al.,

				2003)
	testosterone		~ 10 nM	(Sugiyama et al., 2003)
	thyroxine (T4)	180 nM	~ 50 nM	(Sugiyama et al., 2003)
	reverse triiodothyronine (rT3)		~ 0.01 nM	(Sugiyama et al., 2003)
	triiodothyronine (T3)		~ 1 nM	(Sugiyama et al., 2003)
OATP2A1	arachidonate	96 μM	~ 10 μM	(Kanai et al., 1995)
	6-keto prostaglandine $F_{1\alpha}$	8 μM	~ 1 nM	(Kanai et al., 1995)
	prostaglandine E_1	70 nM		(Kanai et al., 1995)
	prostaglandine E_2	94 nM	~ 0.1 nM	(Kanai et al., 1995)
	prostaglandine $E_{2\alpha}$	104 nM		(Kanai et al., 1995)
	thromboxane B_2	423 nM	~ 1 nM	(Kanai et al., 1995)
OATP2B1	taurocholate	18 μM	~1 μM	(Nishio et al., 2000)
	leukotriene C_4	3 μM	~ 1 pM	(Nishio et al., 2000)
	prostaglandin D_2	18 μM	~ 10 nM	(Nishio et al., 2000)
	prostaglandin E_1			(Nishio et al., 2000)
	prostaglandin E_2		~ 0.1 nM	(Nishio et al., 2000)
	thromboxane B_2		~ 1 nM	(Nishio et al., 2000)
OATP4A1	taurocholate		~ 1 μM	(Fujiwara et al., 2001)
	triiodothyronine (T3)		~ 1 nM	(Fujiwara et al.,

				2001)
OATP4C1	triiodothyronine /T3)	2 μM	~ 1 nM	(Mikkaichi et al., 2004)
OATP6B1	taurocholate	9 μM	~ 1 μM	(Suzuki et al., 2003)
	dehydroepiandrostenone sulfate	26 μM	~ 0.1 nM	(Suzuki et al., 2003)
	thyroxine (T4)	6 μM	~ 50 nM+	(Suzuki et al., 2003)
	triiodothyronine (T3)		~ 1 nM	(Suzuki et al., 2003)
OATP6C1	taurocholate	3 μM	~ 1 μM	(Suzuki et al., 2003)
	dehydroepiandrostenone sulfate	22 μM	~ 0.1 nM	(Suzuki et al., 2003)
	thyroxine (T4)	6 μM	~ 50 nM	(Suzuki et al., 2003)
	triiodothyronine (T3)		~ 1 nM	(Suzuki et al., 2003)
human				
OATP1A2	cholate	93 μM	~ 1 μM	(Kullak-Ublick et al., 1995)
	taurocholate	60 μM	~ 0.1 μM	(Kullak-Ublick et al., 1995)
	glycocholate		~ 0.5 μM	(Kullak-Ublick et al., 1995; Kullak-Ublick et al., 2001)
	taurochenodeoxycholate		~ 0.5 μM	(Kullak-Ublick et al., 1995)

	tauroursodeoxycholate	19	~ 0.001 μM	(Kullak-Ublick et al., 1995)
	bilirubin		~ 10 μM	(Briz et al., 2003)
	estradiol-17β-glucuronide			(Briz et al., 2003; Kullak-Ublick et al., 2001)
	estrone-3-sulfate	16 - 59	~ 2 nM	(Bossuyt et al., 1996b; Lee et al., 2005)
	dehydroepiandrostenone sulfate	7 μM	~ 5 μM	(Kullak-Ublick et al., 1998)
	prostaglandin E_2		~ 1 nM	(Kullak-Ublick et al., 2001)
	reverse triiodothyronine (rT3)		~ 0.1 nM	(Fujiwara et al., 2001)
	triiodothyronine (T3)	7 μM	~ 1 nM	(Fujiwara et al., 2001)
	triiodothyronine sulfate (T3S)		~ 0.1 nM	(van der Deure et al., 2010)
	thyroxine (T4)	8 μM	~ 100 nM	(Fujiwara et al., 2001)
	thyroxine sulfate (T4S)		~ 10 pM	(van der Deure et al., 2010)
OATP1B1	cholate	11 μM	~ 1μM	(Cui et al., 2001)
	taurocholate	10 – 34 μM	~ 0.1 μM	(Abe et al., 1999; Cui et al., 2001; Hsiang et al., 1999)
	glycocholate		~ 0.5 μM	(Kullak-Ublick et al., 2001)
	tauroursodeoxycholate	7 μM	~ 0.001 μM	(Maeda et al., 2006)

	glycoursodeoxycholate	5 μM	~ 0.1 μM	(Maeda et al., 2006)
	bilirubin	8 – 160 nM	~ 10 μM	(Briz et al., 2003; Cui et al., 2001)
	bilirubinmonoglucuronide	100 nM	~ 1 μM	(Cui et al., 2001)
	bilirubindiglucuronide	280 nM	~ 1 μM	(Cui et al., 2001)
	estradiol-17β-glucuronide	4- 14 μM		(Cui et al., 2001; Hirano et al., 2004; Konig et al., 2000b; Nakai et al., 2001; Tamai et al., 2001)
	estrone-3-sulfate	458 nM - 13 μM 68 -94 nM and 5 - 7μM	~ 2 nM	(Cui et al., 2001; Hirano et al., 2004) (Tamai et al., 2001)
	dehydroepianstrostenone sulfate	22 μM	~ 5 μM	(Cui et al., 2001)
	leukotriene C_4		~ 10 pM	(Abe et al., 1999; Kullak-Ublick et al., 2001)
	leukotriene E_4		~ 0.1 nM	(Abe et al., 1999)
	prostaglandine E_2		~ 1 nM	(Abe et al., 1999; Kullak-Ublick et al., 2001; Tamai et al., 2000)
	reverse triiodothyronine sulphate (rT3S)		~ 10 nM	(van der Deure et al., 2008a)
	triiodothyronine (T3)	3 μM	~ 1 nM	(Abe et al., 1999)
	triiodothyronine sulphate (T3S)		~ 0.1 nM	(van der Deure et al., 2008a)
	thyroxine (T4)	3 μM	~ 100 nM	(Abe et al., 1999)

	thyroxine sulphate (T4S)		~ 10 pM	(van der Deure et al., 2008a)
	thromboxane B_2		~ 0.1 nM	(Abe et al., 1999)
OATP1B3	cholate	42 μM	~ 1 μM	(Briz et al., 2006)
	taurocholate	6 - 42 μM	~ 0.1 μM	(Abe et al., 2001; Briz et al., 2006)
	glycocholate	43 μM	~ 0.5 μM	(Briz et al., 2006)
	taurochenodeoxycholate		~ 0.5 μM	(Briz et al., 2006)
	tauroursodeoxycholate	16 μM	~ 0.001 μM	(Maeda et al., 2006)
	glycoursodeoxycholate	25 μM	~ 0.1 μM	(Maeda et al., 2006)
	taurodeoxycholate		~ 0.5 μM	(Briz et al., 2006)
	bilirubin	39 nM	~ 10 μM	(Briz et al., 2003)
	bilirubinmonoglucuronide	500 nM	~ 1 μM	(Cui et al., 2001)
	CCK8	4 - 11 μM	~ 1 pM	(Hirano et al., 2004; Ismair et al., 2001)
	dehydroepiandrostenone sulfate		~ 5 μM	(Konig et al., 2000a)
	estradiol-17β-glucuronide	5 – 25 μM		(Cui et al., 2001; Hirano et al., 2004; Konig et al., 2000a)
	estrone-3-sulfate	73 μM (pH 8.0) 55 μM (pH 6.5)	~ 2 nM	(Leuthold et al., 2009)
	dehydroepiandrostenone sulfate	> 30 μM	~ 5 μM	(Cui et al., 2001)
	glutathione	5 μM		(Briz et al., 2006)
	leukotriene C_4		~ 10 pM	(Konig et al.,

				2000a; Kullak-Ublick et al., 2001)
	prostaglandine E_2		~ 1 nM	(Kullak-Ublick et al., 2001; Tamai et al., 2000)
	triiodothyronine (T3)	6 μM	~ 1 nM	(Abe et al., 2001)
	thyroxine (T4)		~ 100 nM	(Kullak-Ublick et al., 2001)
OATP1C1	taurocholate		~ 0.1 μM	(Leuthold et al., 2009)
	estradiol-17β-glucuronide			(Pizzagalli et al., 2002)
	estrone-3-sulfate		~ 2 nM	(Pizzagalli et al., 2002)
	reverse triiodothyronine (rT3)	128 nM	~ 0.1 nM	(Pizzagalli et al., 2002)
	thyroxine (T4)	90 – 120 nM	~ 100 nM	(Pizzagalli et al., 2002; van der Deure et al., 2008b)
	thyroxine sulfate (T4S)	3 μM	~ 10 pM	(van der Deure et al., 2008b)
	triiodothyronine (T3)		~ 1 nM	(Pizzagalli et al., 2002)
OATP2B1	taurocholate	72 μM (pH 5.0)	~ 0.1 μM	(Nozawa et al., 2004)
	estrone-3-sulfate	5 – 21 μM	~ 2 nM	(Kullak-Ublick et al., 2001; Tamai et al., 2001) (Grube et al., 2006a; Hirano et al., 2006;

				Nozawa et al., 2004; Pizzagalli et al., 2003)
	dehydroepadrostenone sulfate	9 μM	~ 5 μM	(Pizzagalli et al., 2003)
	prostaglandine E_2		~ 1 nM	(Tamai et al., 2000)
	tyroxine (T4)	770 nM (pH 8.0) 310 nM (pH 6.5)	~ 100 nM	(Leuthold et al., 2009)
OATP2A1	prostaglandin D_2			(Lu et al., 1996)
	prostaglandin E_1			(Lu et al., 1996)
	prostaglandin E_2		~ 1 nM	(Kraft et al., 2010; Lu et al., 1996)
	prostaglandin $F_{2\alpha}$		~ 10 pM	(Lu et al., 1996)
	thromboxane B_2		~ 0.1 nM	(Lu et al., 1996)
OATP3A1	estrone-3-sulfate		~ 2 nM	(Tamai et al., 2000)
	prostaglandine E_1	59 mM		(Adachi et al., 2003)
	prostaglandine E_2	56 nM	~ 1 nM	(Adachi et al., 2003)
	prostaglandine F_2			(Adachi et al., 2003)
OATP3A1_v1	estrone-3-sulfate	pH 6.5	~ 2 nM	(Leuthold et al., 2009)
	prostaglandine E1	101 nM		(Huber et al., 2007)
	prostaglandine E2	218 nM	~ 1 nM	(Huber et al.,

				2007)
	tyroxine (T4)		~ 100 nM	
	vasopressin		~ 1 pM	(Huber et al., 2007)
OATP3A1_v2	arachidonate		~ 0.1 nM	(Huber et al., 2007)
	estrone-3-sulfate	pH 6.5	~ 2 nM	(Leuthold et al., 2009)
	prostaglandine E_1	218 nM		(Huber et al., 2007)
	prostaglandine E_2	371 nM	~ 1 nM	(Huber et al., 2007)
	tyroxine (T4)	pH 6.5	~ 100 nM	(Leuthold et al., 2009)
	vasopressin		~ 1 pM	(Huber et al., 2007)
OATP4A1	taurocholate	15 μM	~ 0.1 μM	(Fujiwara et al., 2001)
	estradiol-17β-glucuronide			(Tamai et al., 2000)
	estrone-3-sulfate		~ 2 nM	(Tamai et al., 2000)
	prostaglandine E_2		~ 1 nM	(Tamai et al., 2000)
	triiodothyronine (T3)	1 μM	~ 1 nM	(Fujiwara et al., 2001)
	reverse triiodothyronine (rT3)		~ 0.1 nM	(Fujiwara et al., 2001)
	thyroxine (T4)		~ 100 nM	(Fujiwara et al., 2001)

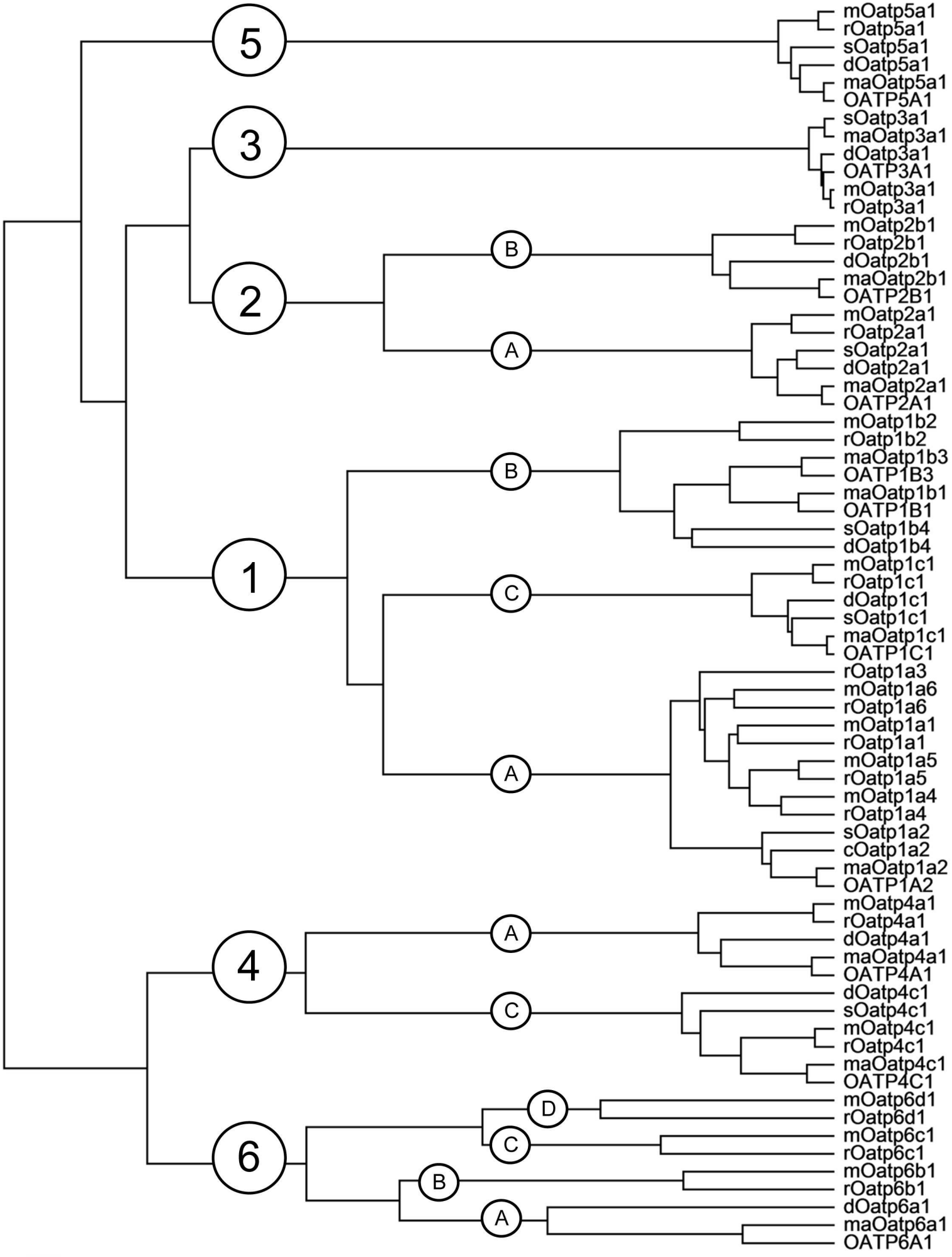
OATP4C1	glycoycholate		~ 0.5 μM	(Yamaguchi et al., 2010)
	chenodeoxycholate		~ 0.5 μM	(Yamaguchi et al., 2010)
	cAMP		~ 10 nM	(Mikkaichi et al., 2004)
	estrone-3-sulfate	27 μM	~ 2 nM	(Yamaguchi et al., 2010)
	triiodothyronine (T3)	6 μM	~ 1 nM	(Mikkaichi et al., 2004)
	tyroxine (T4)		~ 100 nM	(Mikkaichi et al., 2004)

Figure legends

Figure 1: Phylogenetic tree and classification of 70 members of the OATP/*SLCO* superfamily of transporters. Human (all capitalized OATP), monkey (maOATP), dog (dOATP), pig (sOATP), rat (rOATP) and mouse (mOATP) proteins are grouped into families (with more than 40% amino acid sequence identity) and subfamilies (with more than 60% amino acid sequence identity).

Figure 2: Distribution of OATPs in selected human epithelial tissues. The OATPs within the same subfamily are labelled with the same color. For more details see text.

Figure 3: Topology models for OATP1B1. A) The predicted secondary structure model for OATP1B1 is shown with 12 transmembrane domains. The extracellular conserved cysteine residues are labelled in black. B) Homology modelling was performed as described (Roth et al., 2012) based on the *E. coli* glycerol-3-phosphate transporter. OATP1B1 is shown from the extracellular side (left) and from within the lipid bilayer (right). Colors of the transmembrane domains match the colors used in the secondary structure model.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A
1
B
C
A
4
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C
6
D
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sOatp5a1
dOatp5a1
maOatp5a1
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OATP3A1
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maOatp1a2
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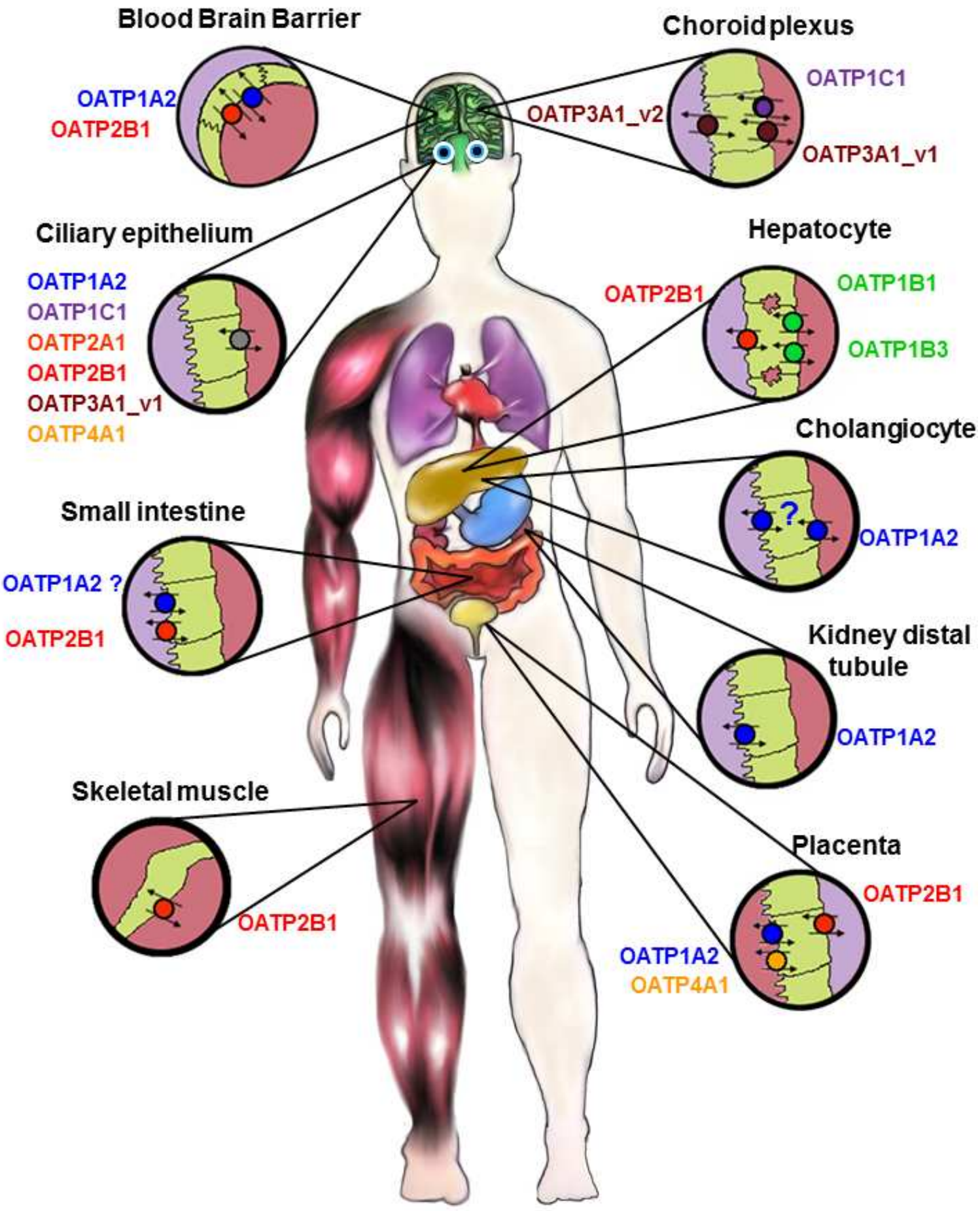
OATP6A1


Blood Brain Barrier
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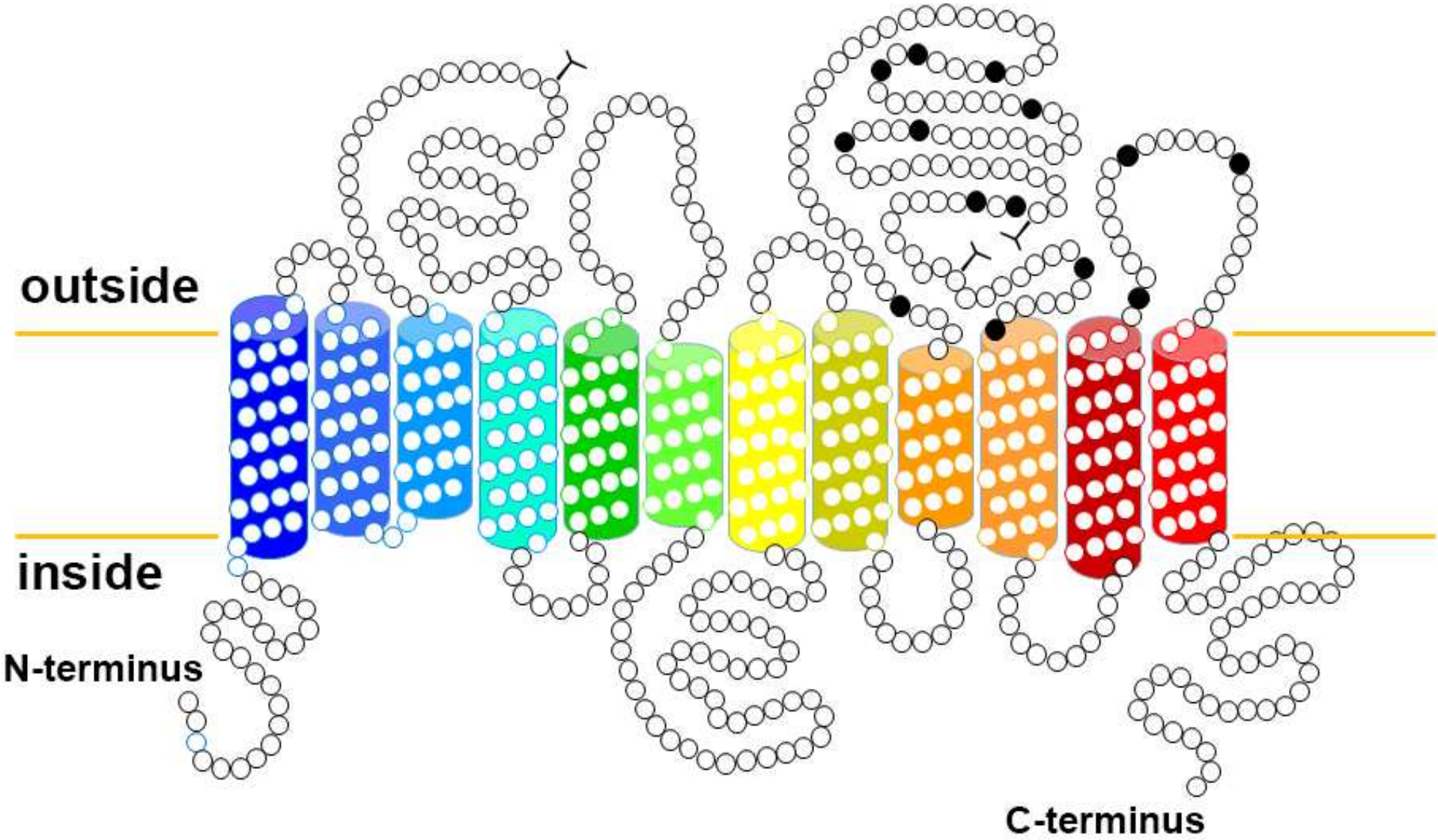
OATP2B1
Choroid plexus
OATP1C1
OATP3A1_v2
OATP3A1_v1
Ciliary epithelium
OATP1A2
OATP1C1
OATP2A1
OATP2B1
OATP3A1_v1
OATP4A1
Hepatocyte
OATP2B1
OATP1B1
OATP1B3
Cholangiocyte
?
OATP1A2
Small intestine
OATP1A2 ?
OATP2B1
Kidney distal tubule
OATP1A2
Skeletal muscle
OATP2B1
Placenta
OATP2B1
OATP1A2
OATP4A1

A



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